Food Intolerance in Humans

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IT IS WELL KNOWN that deficient intake of protein, calories, vitamins or minerals leads to a variety of nutritional disorders. It is known that food contaminated with toxic materials or microorganisms may cause illness if consumed. It is also known that certain foods naturally contain nonnutrient poisonous substances that may cause illness and in some cases, death. Nevertheless, it is not generally realized that the nutrient components of food, in themselves, may be toxic for certain people, causing illness or aggravating preexisting illness.

Food intolerance may be defined as any illness or biochemical or metabolic abnormality that is causally connected to the ingestion of any food or dietary component. An illness that is causally connected to a *nonnutritive* dietary component may be referred to as food poisoning or food toxicity. The term food intolerance is usually applied to illness resulting from the ingestion of substances that have *nutritive* value such as carbohydrates, lipids, proteins and amino acids. Logically speaking, vitamins, minerals, water and oxygen are nutrients and under certain circumstances may cause illness. Water and oxygen are not usually thought of as food although there is no question that they are vital nutrients. In addition, one should add purines to the list of nutrients capable of aggravating preexisting disease, although they are dispensible nutrients.

There may be an obvious connection between food ingestion and the production of acute illness or a less obvious connection so that a patient may fail to recognize the relationship between his disease and the offending dietary component.

Under special circumstances certain combinations or amounts of food substances may cause illness in otherwise healthy persons. For example, fasting followed by refeeding may result in gastrointestinal symptoms and edema due to sodium retention. This is an example of food intolerance which can occur in otherwise healthy persons. Many illnesses may cause anorexia and may lead to nausea and vomiting when eating is attempted. This type of food intolerance may be considered to be a secondary type since the food is not toxic but the illness has so altered the normal physiology that the patient becomes intolerant to many types of foods. Primary disorders of smell and taste may cause the patient to reject food as unpalatable. Psychological disturbances, cultural habits, personal preferences, religious edicts and the like may render certain foods unacceptable to certain persons or groups of people. This is a difficult area to study but a most important one. Food manufacturers especially are aware of these psychological problems and attempt to engender psychological acceptability for their products in consumers.

We must also consider foods that are toxic for some people for reasons that are not clear. Often allergy or psychological aversion is invoked to explain the sensitivity or distaste a person has for a particular food. Although both food allergies and psychological aversions are well known to exist, these are often not adequate explanations for the illnesses that follow the ingestion of cer-

tain foods. Therefore, there are many foods that are toxic for some people for unknown reasons.

In this paper we shall consider only those food intolerances that are related to nutrients but not those that are caused by nonnutrient substances that are endogenously produced within food or that are exogenously produced and enter somehow into the food.

Definitions

The following definitions are used:

• A chemical is any substance with a defined structure and specific properties.

• A metabolite is any chemical that is transformed into one or more derivatives by the metabolic processes of the body. Physiological and nonphysiological substances that are transformed or metabolized by the body are metabolites. Certain substances may be absorbed and retained or excreted in unchanged form (or both). Such materials would not be considered to be metabolites and may be nontoxic unless they occupy space thereby interfering with normal function. Such substances although not metabolized may bind to proteins or cell membranes or may be transported through cell membranes. In some cases chemically inert radioactive substances are stored by tissues and prove to be toxic because of their radioactivity. Certain substances are not absorbed or altered and pass through the gastrointestinal tract unchanged while others are metabolized only by the gastrointestinal flora.

• A nutrient is any chemical that is utilized by the body to produce energy or a cellular structure either directly or indirectly. Although water and oxygen are essential nutrients the toxic effects of each will not be considered.

• An essential nutrient is one that is not synthesized at all or only partially by the metabolic processes and leads to recognizable illness when totally excluded from the diet.

• A nonessential nutrient is one that can be synthesized by the metabolic processes of the body but can also be supplied by the diet. Total exclusion of a nonessential nutrient from the diet does not lead to any recognizable illness. Both essential and nonessential nutrients are metabolites.

• Food is any nutrient or mixture of nutrients and other chemicals that is eaten and processed in the digestive system. This processing includes mastication, swallowing, digestion, absorption, in-termediary metabolism and excretion. Food may be relatively simple and pure chemically (such as sodium chloride or sucrose) or extremely complex, being composed of a great variety of substances all of which may not be known (such as chocolate layer cake, milk, eggs or oranges). In complex foods the amount of any given component may vary at different times. Food, in addition to one or more nutrients, may contain metabolites, nondigestible substances, endogenously produced substances (such as flavor and aroma-producing substances, caffeine and other drug-like agents) and exogenously added substances (coloring agents, emulsifiers, antibiotics, antioxidants and so forth). One must distinguish between nutrients and foods. Not all nutrients are considered to be foods—water and oxygen, for example.

• Pseudofoods are certain substances that are considered to be food items in spite of the fact that they contain few if any nutrients. These substances may contain many chemicals some of which have potent physiological effects and may be considered to be drugs. In this category belong coffee, tea, chocolate, spices and herbs.

• A drug or medication is any chemical that is administered to a patient to produce a therapeutic effect. Drugs may be either physiological or nonphysiological substances either derived from natural sources or from synthetic processes. Drugs may be administered in nonphysiological doses and through nonphysiological routes.

• Ethanol is a simple alcohol which in smaller amounts is a nonessential nutrient providing calories (7.07 kcal per gram) and in larger amounts is a drug that produces its well-known intoxicating effects acutely and pathological effects after long-term use. Because of the tax laws its use is regulated by the United States Department of the Treasury rather than the Food and Drug Administration and the toxic effects are studied by the National Institute on Alcohol Abuse and Alcoholism which is part of the Alcohol, Drug Abuse, and Mental Health Administration of the United States Public Health Service.

Classification of Food Intolerance

Food intolerance is classified as shown in Table 1. Many nonnutrient substances can cause a large variety of illnesses. Substances not part of a particular food may enter into the food while in its natural state. Substances may be added to foods during processing or may enter into foods from

TABLE 1.—*Classification of Food Intolerance*

Nonnutrient substances
    Exogenous substances
    Endogenous substances
Nutrient substances
    Carbohydrates
    Proteins and amino acids
    Lipids
    Minerals
    Vitamins
    Purines
    Water
    Oxygen
Multiple food intolerances
Idiopathic food intolerance

TABLE 2.—*Carbohydrate-Induced Food Intolerance*

Glucose-galactose intolerance due to glucose-galactose malabsorption
Lactose intolerance due to lactase deficiency
Sucrose-starch intolerance due to sucrase-isomaltase deficiency
Sucrose-fructose intolerance (hereditary fructose intolerance) due to fructose-1-phosphate aldolase deficiency
Sucrose-fructose-glycerol intolerance due to fructose diphosphatase deficiency
Galactose intolerance
    Galactosemia due to uridyl transferase deficiency
    Cataracts due to galactokinase deficiency
    Galactose intolerance after ethanol ingestion
Trehalose intolerance due to trehalase deficiency
Starch intolerance due to α-amylase deficiency
Carbohydrate intolerance
    Reactive hypoglycemia
    Hyperlipoproteinemia (type IV)
    Glucose intolerance and hyperinsulinemia
    Obesity
    Precipitation of paralysis in familial hypokalemic periodic paralysis especially after exercise
    Gastrointestinal maladaption syndrome related to failure of jejunal glycolytic enzyme adaptation to dietary carbohydrate
        Primary
        Secondary
    Postoperative dumping syndrome
    Lactic acidosis due to pyruvate dehydrogenase deficiency
    Dental caries related to sucrose and Streptococcus mutans
Raffinose-stachyose-verbascose intolerance due to indigestibility

bacteria, molds or fungi growing on the food. Chemical substances or microorganisms may contaminate food. An animal may eat a plant or another organism and thereby acquire a toxic substance. These are exogenous nonnutrient substances. On the other hand, a food source may produce substances by virtue of its own metabolism that are toxic when ingested. Such substances may be toxic for all persons or may be toxic only for some persons by virtue of some metabolic condition or the use of a particular drug. These substances are endogenous nonnutrient substances. It is not possible in this paper to consider the food intolerances caused by nonnutrient substances because of the large number of such substances and their diverse effects.

Food intolerance is caused by nutrient substances. Although purines, water and oxygen can cause illness in the appropriate circumstances, we shall consider mainly those disorders related to carbohydrates, amino acids and proteins, lipids, minerals and vitamins.

There are numerous medical conditions in which many different foods cause symptoms. These can be considered in the category of multiple food intolerances. The symptoms may be either a nonspecific portion or a dominant aspect of a particular disease. Anorexia as part of an acute illness is well known but the mechanism is often obscure. Patients may desire little if any food and attempts to eat may lead to nausea and vomiting. On the other hand, in anorexia nervosa the patients may eat small amounts of food but not enough to maintain normal weight. In some instances a person may be intolerant of a great variety of foods. A patient with anosmia or dysgeusia may be poorly tolerant of all foods because of the disturbance of smell and taste. Here the reason for food intolerance is apparent although

the basic disorder of smell and taste is usually unknown. In this regard the problem of anorexia and zinc deficiency is considered elsewhere in this symposium.

A final category of food intolerance is the idiopathic variety. Usually the person becomes ill after eating a particular food. The offending substance may not be known. Allergic or idiosyncratic mechanisms may be invoked but such semantic explanations are not very helpful. This category of food intolerance merely serves to alert the investigator that a particular food can cause illness and, therefore, is a prime target for investigation.

Carbohydrate-Induced Food Intolerance

Table 2 lists disorders related to various carbohydrates. *Glucose-galactose intolerance* occurs infrequently in infants.[1,2] Because of the inability to absorb these sugars an osmotic diarrhea occurs. It is presumed that there is a defect in the glucose-galactose carrier protein in the small intestinal mucosal epithelial cells.[3] Renal glycosuria also is

seen in this condition presumably because of a similar carrier protein defect. The condition may be treated by restricting glucose and galactose in the diet and using fructose as a source of dietary carbohydrate.[4-7]

Lactose intolerance is most common.[8-15] Most people in the world are lactase deficient. Therefore, milk intolerance is not uncommon because of the lack of the jejunal brush border enzyme, lactase. In lactase deficiency the lactose of milk cannot be hydrolyzed and an osmotic diarrhea occurs together with fermentation of the lactose by intestinal microorganisms. Lactase deficiency may occur at an early age or may occur at variable ages in different persons. Lactose intolerance, therefore, may be present at birth or may occur late in life. Treatment requires the avoidance of lactose by restricting dietary milk and milk-containing products. Lactose intolerance should not be confused with milk allergy which is related to milk proteins. This will be discussed in the section on amino acid-induced and protein-induced food intolerance.

Sucrose-starch intolerance is a rare entity. This is caused by a deficiency of two jejunal brush border enzyme activities, sucrase and isomaltase.[16,17] Each of the enzyme activities is contained at a different site within one polypeptide molecule[18] which serves as a multifunctional enzyme.[19] A deficiency of these enzyme activities leads to failure of hydrolysis of sucrose and the isomaltose derived from the digestion of starch. The unhydrolyzed sucrose and isomaltose cause an osmotic diarrhea and are also fermented by intestinal bacteria. Therapy requires the restriction of dietary sucrose and starch. Fructose also may be used to treat this condition[20] because fructose can increase the activity of sucrase and isomaltase.[21] In one patient with sucrase-isomaltase deficiency given dietary fructose the enzymes increased in activity, although not to normal levels, and increased the tolerance of the patient to dietary sucrose.[20]

Sucrose-fructose intolerance occurs in the disease hereditary fructose intolerance.[22] In this condition the enzyme fructose-1-phosphate aldolase is lacking in various tissues, notably the liver. Ingestion of sucrose or fructose leads to the accumulation of fructose-1-phosphate in the liver and other tissues and results in hypoglycemia.[23] This may be so severe that shock and death may occur. Treatment involves restricting dietary sucrose and fructose. It is possible to increase the

activity of fructose-1-phosphate aldolase by the oral administration of folic acid in pharmacological doses.[24] The enzyme activity increases to higher levels although it does not reach normal values. Folic acid has been found to increase the activities of glycolytic enzymes of the jejunum and liver although the mechanism of action is not clear.[25,26] Fructose-1,6-diphosphate aldolase activity is diminished in this condition although there is sufficient activity for normal function.[22] Both fructose-1-phosphate aldolase and fructose-1,6-diphosphate aldolase activities are contained within a single polypeptide chain although each activity resides in a different region.[27] This single polypeptide is another example of a multifunctional enzyme.[19] It is of interest that persons with hereditary fructose intolerance rarely have dental caries because they quickly learn to avoid dietary sucrose strictly.[22]

Sucrose-fructose-glycerol intolerance occurs in persons with fructosediphosphatase deficiency.[28-30] This enzyme is critical for the function of the gluconeogenetic pathway in the liver.[30] A deficiency of this enzyme may result in chronic hypoglycemia,[29] ketotic hypoglycemia[28] or in a rare case, reactive hypoglycemia.[30] Hypoglycemia can be provoked by sucrose, fructose, glycerol, ethanol, a ketotic diet and fasting (such as may occur in an anorectic illness). Treatment involves restriction of sucrose, fructose and glycerol, and frequent feedings with glucose in the chronic hypoglycemic form of the disease.[28-30] Folic acid may increase the activity of fructose-diphosphatase and thereby improve the blood glucose levels in the chronic hypoglycemia form of the disease[29] and may protect those patients with the milder forms of the disease.[28,30]

Galactose is toxic in galactosemia in which the enzyme uridyl transferase in the galactose metabolic pathway is deficient.[31,32] The lactose of milk, when hydrolyzed, yields glucose and galactose. Galactose in the diet is provided almost exclusively from milk and milk products. Ingestion of galactose results in the accumulation of galactose-1-phosphate in the tissues of several organs including the liver, kidney and lens of the eye.[31,32] Continued accumulation causes hypoglycemia, cataracts, mental retardation, growth retardation, and hepatic and renal damage. Ultimately the condition ends fatally.[31] Treatment consists of galactose restriction by the elimination of milk and milk-containing products from the diet.[31,32] In addition to the "classical" form of the galac-

tose-1-phosphate uridyl transferase variant which is responsible for the first recognized severe form of galactosemia, at least five additional variant forms of the enzyme have been described.[33] Two of the variants (Duarte and Los Angeles) cause no clinical manifestations in the homozygous form, one may cause mild symptoms ("Negro"), and three are associated with severe symptoms of galactosemia (classical, Indiana, Rennes). Galactose may cause blurred vision in normal persons when given in amounts that greatly exceed the usual dietary levels. Administration of 450 grams of galactose per day to normal persons caused blurred vision due to edema of the lens.

Ingestion of galactose by persons with *galactokinase deficiency* results in cataracts but none of the other clinical manifestations seen in galactosemia.[34-36] Galactokinase deficiency is also treated by eliminating milk and milk-containing products from the diet. The ingestion of ethanol impairs the activity of an enzyme, 4'-epimerase,[37] which is another enzyme in the galactose metabolic pathway. Therefore, galactose tolerance becomes abnormal if galactose is administered after the consumption of ethanol.[38,39] In animals a combination of ethanol and galactose feeding is more lethal than either alone.[40]

Vomiting and diarrhea have been reported in one family after they ate mushrooms.[41] The symptoms disappeared in one day. The mushroom intolerance was secondary to the *deficiency of jejunal trehalase,* a brush-border disaccharidase. Mushrooms contain a disaccharide, trehalose, which cannot be hydrolyzed in trehalase deficiency and, therefore, causes an osmotic diarrhea.

Starch intolerance has been described in patients with a selective deficiency of pancreatic α-amylase.[42,43] Diarrhea occurred as a consequence of the fermentation by gastrointestinal flora of undigested starch. It was suggested[43] that there was late maturation of the biosynthetic mechanism for the pancreatic amylase. The exact molecular nature of the amylase deficiency is unknown. Treatment consisted of eliminating starch from the diet.

A high carbohydrate diet, in general, may be related to a number of medical problems. A high carbohydrate diet may be involved with reactive hypoglycemia.[44] Reactive hypoglycemia can be classified as diabetic, alimentary, hormonal (hypothyroidism, Addison disease), or idiopathic in type.[44] In a rare case fructosediphosphatase deficiency may cause "idiopathic" reactive hypo-

glycemia.[30] In many patients with the so-called type IV hyperlipoproteinemia, panhyperlipemia may develop as a consequence of a high carbohydrate diet.[45-51] The panhyperlipemia may decrease when their high carbohydrate diet is restricted. Maturity onset diabetes usually is associated with a high carbohydrate diet. Early, an abnormal glucose tolerance and hyperinsulinemia occur.[52-57] Restriction of the high carbohydrate diet may bring the glucose tolerance and serum insulin levels to normal.[53-55] Obesity is very common in maturity-onset diabetes.[52-57] Obesity, of course, is a consequence of long-term high carbohydrate ingestion, which generally is the source of the excess calories that gave rise to the obesity.[58] This problem is considered in more detail elsewhere in this symposium. A high carbohydrate intake, especially when combined with exercise, may precipitate paralysis in familial hypokalemic periodic paralysis.[59]

The *feeding of glucose and fructose to normal persons* results in an increase in the activities of various jejunal epithelial glycolytic enzymes and a decrease in the activity of fructosediphosphatase.[26,60] There are patients who have chronic intermittent diarrhea or a dumping-like syndrome,[61] or both, with no known cause. Careful and extensive study in these patients has failed to show any intestinal lesion or any other disease. The administration of glucose and fructose to these patients provokes their symptoms. Small intestinal tissue obtained by peroral biopsy[62] for analysis of glycolytic enzyme activities has shown failure of the normal adaptive enzyme response.[61] In many of these patients the condition often improves when they receive a low carbohydrate diet.[61] The nature of this type of carbohydrate intolerance is unknown but has been termed the gastrointestinal maladaptation syndrome.

In patients with histological abnormalities of the small intestine the normal adaptive response of the glycolytic enzymes may be lost. Successful treatment of the small intestinal disease results in the return of the normal adaptive response. This sequence of events has been found to occur in *tropical sprue.*

Persons who have been starving or have been subsisting on a *low carbohydrate diet* show a decrease in the activities of their jejunal glycolytic enzymes. Acute administration of carbohydrate in the form of glucose may cause diarrhea or other gastrointestinal symptoms.

Carbohydrate feeding after gastrointestinal re-

section may lead to the so-called *dumping syndrome*.[63,64] The mechanism of the dumping syndrome is unclear.

In patients with the rare disease *pyruvate dehydrogenase deficiency*, an increased carbohydrate intake may cause lactic acidosis.[65-67] In such patients the lactic acidosis can be ameliorated by restricting dietary carbohydrate.

The occurrence of *dental caries* is a very common condition which is related to the ingestion of refined sugar.[68-71] A gelatinous material, plaque, forms on teeth and becomes colonized by bacteria, mainly Gram-positive streptococci. Plaque is composed of oral microorganisms and an extracellular matrix of bacterial polysaccharides, leukocytes, salivary glycoproteins, water and epithelial cell remnants.[69,70] Sugars, especially sucrose, promote the formation of plaque.[69] Sucrose promotes the formation of dextrans by and the colonization of plaque by Streptococcus mutans which is considered to be a primary microbial agent of plaque.[69] The acid produced by the plaque bacteria erodes the teeth and forms dental caries.[69] Bacterial and leukocytic enzymes may also degrade the organic components of enamel and dentine.[69,70] In those societies in which refined sugar (sucrose) is not used dental caries rarely occur.[68] Dental caries cannot be induced in germ-free animals no matter how cariogenic their diet may be.[72] However, the view that sucrose is cariogenic is not accepted by all investigators.[73,74]

Certain plants contain *polysaccharides* which are poorly digested in the small intestine.[75] These sugars, raffinose, stachyose and verbascose, are not hydrolyzed but are fermented by Clostridium perfringens,[76] which is a part of the normal gastrointestinal flora. The fermentation can result in a great deal of flatulence which can cause much discomfort.[77]

Protein-Induced and Amino Acid-Induced Food Intolerance

Proteins and amino acids can be toxic in various illnesses. Table 3 lists many of these conditions.

Protein-Induced Food Intolerance

Celiac disease results from sensitivity to the protein, gluten, contained in wheat, rye, oats and barley.[78] The reason why gluten causes small intestinal damage is not known. Strict avoidance of gluten is necessary in the treatment of this condition. In some adult patients there may be

no response to the elimination of gluten from the diet.[79,80] In dermatitis herpetiformis lesions of the gastrointestinal tract resembling those seen in gluten enteropathy may occur. The affected persons may or may not be symptomatic.[81-83] A

TABLE 3.—*Protein-Induced and Amino Acid-Induced Food Intolerance*

Protein-induced food intolerance

Gluten intolerance
  Celiac disease (gluten enteropathy)
  Dermatitis herpetiformis
  IgA deficiency and diarrhea
  Mastocytosis
Protein intolerance
  Food allergy
    Milk protein allergy
    Soy bean protein toxicity
  Hepatic encephalopathy in cirrhosis especially in porto-systemic shunting
  Renal failure
  Pancreatic insufficiency
  Enterokinase deficiency
  Urea cycle enzyme defects
    Ornithine transcarbamylase deficiency
    Argininosuccinic acid synthetase deficiency
    Argininosuccinate lyase deficiency
    Carbamyl phospate synthetase deficiency
    Arginase deficiency
  Lysine-ornithine-arginine malabsorption
  Cystine-lysine-arginine-ornithine transport defect (cystinuria)
  Homocystinuria
  Succinyl-CoA:3-ketoacid CoA-transferase deficiency
  Avidin binding of biotin

Amino acid-induced food intolerance

Tryptophan intolerance
  Hartnup disease
  Tryptophan malabsorption (blue diaper syndrome)
Phenylalanine intolerance (phenylketonuria)
Leucine-isoleucine-valine intolerance (maple-syrup-urine disease)
Valine intolerance (hypervalinemia)
Leucine-isoleucine intolerance (hyperleucine isoleucinemia)
Lysine intolerance (persistent hyperlysinemia)
Methionine intolerance (methionine malabsorption syndrome or oasthouse urine disease)
Leucine-induced hypoglycemia
Monosodium glutamate intolerance (Chinese restaurant syndrome)
Valine-isoleucine-threonine-methionine-thymine-propionate intolerance
  Propionic acidemia
  Methylmalonic aciduria
Isovaleric acidemia
β-Methylcrotonylglycine, β-hydroxyisovalericaciduria
α-Methylacetoacetic α-methyl-β-hydroxybutyricaciduria
Hereditary tyrosinemia
Histidinemia
Hyperprolinemia

gluten-free diet may be helpful in some but not all of these patients. In some patients with selective IgA deficiency and diarrhea a gluten-free diet may be effective therapy.[84] The exact relationship between IgA deficiency and the diarrhea is unknown. In one patient with mastocytosis involving the small intestine a gluten-free diet was effective in the treatment of otherwise intractable diarrhea.[85]

It is known that a variety of food proteins (such as milk, egg and wheat) can cause *allergic reactions* in susceptible people.[86-91] Often, however, definitive proof of protein allergy is lacking and such diagnoses must be considered to be presumptive. This is particularly the case when nonspecific symptoms outside of the gastrointestinal tract are attributed to a poorly defined "food allergy." The relief of symptoms by use of an elimination diet does not prove the allergic mechanism or identify the offending foods or proteins. When a particular food consistently causes gastrointestinal symptoms the possibility of an allergic reaction must be considered. However, even in these circumstances, definitive proof generally is lacking. Many foods cause urticaria, asthma and other problems, but generally the offending substance in the food has not been identified, and, again, attributing the cause to an allergic reaction is only presumptive. For example, various foods may contain substances such as tartrazine which is a common food color additive. Tartrazine may cause urticaria and asthma. It may or may not be associated with aspirin intolerance.[92] The occurrence of urticaria or asthma may be attributed to the proteins of a particular food when in fact they may be due to sensitivity to substances such as tartrazine which are added to food. The exact biochemical nature of tartrazine sensitivity is unknown. Nevertheless, there appear to be many instances in which protein allergy seems to be a reasonable possibility.[89]

In *milk allergy,* vomiting, chronic diarrhea and failure to thrive occur.[86,93-95] Malabsorption develops and eczema and eosinophilia are common. The symptoms can be reproduced with oral ingestion of milk. Allergy to cow's milk is said to be more common in atopic infants and their families than in the population at large.[96] The onset of the condition is at about one month of age. The sensitivity to milk may disappear at the age of 1 to 1½ years. Sodium cromoglycate has been used to treat milk allergy.[97]

Cases of patients with *soy bean toxicity* have been described. In a 6-week-old child, villus flattening and malabsorption developed after the ingestion of soy bean protein. Avoidance of the soy bean protein led to improvement and reingestion caused the return of the symptoms and histological abnormalities. Although an allergic reaction was considered as a possibility the authors noted that definitive proof was lacking.[98]

Patients with *food allergies* have been described although the nature of the protein to which the patient is allergic remains unknown. The case of a patient with an urticarial reaction to ingested fruit has been described.[99] In this patient vomiting also developed and sometimes diarrhea also occurred after fish was eaten. The patient's condition did not respond to therapy with sodium cromoglycate.

Eosinophilic gastroenteritis with diarrhea, peripheral eosinophilia, and eosinophilic infiltration of the small intestine has been described.[100,101] At least in one of the patients an allergic mechanism seemed to be a reasonable explanation.[100] Corticosteroid therapy is effective in this disease[100,101] but sodium cromoglycate administration is not.[101]

Protein intolerance is manifested by *hepatic encephalopathy* in cirrhosis of the liver especially if portosystemic shunting is present.[102,103] The diversion of blood away from the abnormal liver results in hyperammonemia. A low protein diet and administration of antibiotics to decrease the ammonia-producing flora of the gastrointestinal tract are necessary to control this condition.[102,103]

In *renal failure* with azotemia a normal protein intake adds to the azotemic burden.[104-106] A low protein diet is necessary if hemodialysis is not used. More recently the keto-acid analogues of essential amino acids have been used in the treatment of chronic renal failure.[107]

In *pancreatic insufficiency* there is a general deficiency of proteolytic enzymes which results in failure of protein hydrolysis and consequent protein malabsorption.[108] Replacement of pancreatic proteolytic enzymes with a suitable enzyme preparation is the proper therapy.[109-111]

In the rare condition *enterokinase deficiency* there is failure of activation of trypsinogen and chymotrypsinogen.[112-114] Consequently, there is failure of digestion of protein in the small intestine and protein malabsorption results. Enterokinase is an enzyme of the small intestine. There are data to suggest that the activation of trypsinogen to trypsin and chymotrypsinogen to chymotrypsin occurs at the surface of the small intestinal epi-

thelial cell.[115] However, the exact localization of enterokinase is not certain. Recent studies suggest that enterokinase activity in the intestines of rats is mainly in a free form in intestinal mucin and is present only to a negligible extent in the brush border.[116] The condition can be difficult to diagnose.[113] Treatment is effected with pancreatic extract.

There is a large number of *disorders of amino acid metabolism*. Many of these diseases involve defects in amino acid transport[117] and enzyme deficiencies. In many instances these defects render the affected person susceptible to dietary protein or specific amino acids, or both. Restriction of dietary protein or specific amino acids may correct some or all of the biochemical abnormalities and clinical manifestations of the disease. Additional measures may be helpful or the treatment of choice. Since dietary protein or amino acids in the usually recommended amounts aggravate the condition these disorders represent protein and amino acid intolerances. Not all disorders of amino acid metabolism are aggravated by normal protein or amino acid intakes or helped by dietary restriction. These amino acid disorders will not be covered here. Many amino acid disorders are exceedingly rare with only one or two patients described and with no information available about the effect of diet on the clinical or biochemical manifestations of the disorder. These disorders also will not be discussed.

Defects of *urea cycle enzymes* (ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinate lyase, carbamyl phosphate synthetase, arginase) result in hyperammonemia with normal protein intakes.[118] The hyperammonemia results from the decreased ability of the liver to handle the ammonia derived from the dietary amino acids. Hyperammonemia is manifested by irritability, ataxia, lethargy, coma and mental retardation. Different defects of the urea cycle enzymes have varying degrees of severity. A low protein diet may be successful, but not always, in treating this group of diseases.

A defect involving the kidney and small intestine in the absorption of basic amino acids (lysine, ornithine, arginine) has been termed *hyperdibasic-aminoaciduria*.[119-121] In this condition lysine competed with arginine transport. The disease is manifested by diarrhea, periodic hyperammonemia, vomiting and malaise. A low protein diet controls the manifestations of the disease but may lead to growth failure and central nervous

system abnormalities. Supplementation with citrulline plus lysine has been reported to be beneficial together with a low protein diet.[121]

In *cystinuria* there is an increased urinary excretion of cystine, lysine, arginine and ornithine with the formation of cystine renal tract calculi. The defect is related to defective transport of these amino acids in the small intestine and kidney.[122] Treatment consists of maintaining a high urine volume[122] and therapy with pencillamine[124] which forms a mixed disulfide with cystine. A low protein[125] or low methionine diet[126] may decrease urinary cystine but not all investigators have been able to show this result.[127]

Homocystinuria[128,129] is characterized by elevated plasma concentrations of methionine and homocystine and increased urinary homocystine excretion. Less constant features are mental retardation, fair complexion and growth failure.[129,130] Dislocation of the lens is common. Arterial and venous thromboses are a major cause of death.[130] Homocystinuria is the result of at least three separate enzyme deficiencies.[130] Cystathionine synthase deficiency is the most common cause of homocystinuria. A deficiency in the formation of deoxyadenosylcobalamin and methylcobalamin leads to a combination of homocystinuria and methylmalonic aciduria. Homocystinuria can also occur when there is a deficiency of methylene tetrahydrofolate reductase. A low-protein low-methionine diet can reduce the elevated plasma methionine and decrease the plasma homocystine especially when supplemented with cystine[131] although cystine may not be required in those patients with residual enzyme activity. Although this dietary approach is encouraging in preventing mental retardation and ectopia lentis in infants it does not repair the dislocated lens and the mental retardation in older children. Pharmacological doses of vitamin B_6 (250 to 500 mg per day)[132] eliminate the chemical abnormalities in many but not all patients with cystathionine synthase deficiency.[130] In the vitamin B_6-responsive form of disease this is the treatment of choice. Treatment of the other types of homocystinuria is discussed in the section on methylmalonic aciduria.

One patient with *succinyl-CoA:3-ketoacid CoA-transferase deficiency* has been reported. This enzyme deficiency was discovered in an infant who had severe, intermittent ketoacidosis. The episodes of severe ketoacidosis were precipitated by either an acute infection or by the ad-

ministration of protein. With glucose alone the infant did well and had minimal ketonuria. The patient died of pneumonia at 6½ months of age.[133]

Raw egg white contains a protein termed avidin which binds biotin tightly. Chronic ingestion of raw egg white can produce biotin deficiency.[134] Avidin is denatured when egg white is cooked and loses its ability to bind biotin.

Amino Acid-Induced Food Intolerance

Hartnup disease results from tryptophan malabsorption which in turn leads to cerebellar ataxia, an intermittent photosensitive pellagra-like rash and mental retardation.[135] It has been suggested that the decreased absorption of tryptophan leads to increased indole formation which inhibits nicotinamide synthesis from tryptophan. The nicotinamide deficiency further depresses tryptophan absorption.[136] Treatment with nicotinamide ranging in dosage from 40 to 250 mg per day has resulted in pronounced clinical improvement.[137]

In *tryptophan malabsorption* (the blue diaper syndrome) there is abnormal small intestinal absorption of dietary tryptophan.[138] There is increased production of indican and indoles which appear in the urine. One of the indoles, indigo blue, is responsible for the blue color of the diapers.

Phenylketonuria is caused by a deficiency of hydroxylation of phenylalanine to form tyrosine.[139] Various metabolities of phenylalanine accumulate and mental retardation[140] results although the exact mechanism is unknown. Treatment consists of providing a low phenylalanine diet in order to prevent hyperphenylalaninemia and the accumulation of the presumably toxic metabolites.[140] Care must be taken not to give a diet too low in phenylalanine since phenylalanine deficiency may impair protein synthesis.

A milder form of phenylketonuria has been described in which a higher phenylalanine intake can be tolerated. In classical phenylketonuria, plasma phenylalanine levels can be kept below 1 mM by providing 250 to 500 mg per day of phenylalanine. As noted, in the milder form a higher phenylalanine intake can be tolerated.[141] The reason for this increased tolerance for phenylalanine is unknown.

Another variant form exists secondary to a deficiency of dihydropteridine reductase which generates the pteridine cofactor (tetrahydrobio-

pterin) necessary for phenylalanine hydroxylase function.[142,143] In one patient, despite prompt treatment with a low phenylalanine diet and excellent control of serum phenylalanine, progressive intractable seizures occurred. Enzyme deficiency was shown in the brain, liver and skin fibroblasts.

Classical phenylketonuria and its variants must be distinguished from transient phenylketonuria,[144] hyperphenylalaninemia without phenylketonuria[145] and transient neonatal hyperphenylalaninemia.[146]

Maple-syrup-urine disease (MSUD) results from a defect in the metabolism of the keto-acid analogues of the branched-chain amino acids (leucine, isoleucine, valine) due to an abnormality of the multienzyme complex (failure of oxidative decarboxylation) which is involved in the metabolism of these keto-acid analogues.[147] The presence of these compounds in the urine gives rise to the odor of maple syrup. In the severe or classical form there are feeding difficulties, vomiting, hypertonicity and a shrill cry in the first week of life. Flaccidity and apnea may occur. Deep tendon reflexes may disappear. Convulsions occur and death may happen early in life. Untreated children have physical and mental retardation.[148,149] Therapy requires severe dietary restriction of branched-chain amino acids from early postnatal life.[150]

The intermittent form of MSUD occurs in late infancy or childhood. Intermittent episodes of illness occur which may be severe. There are lethargy, vomiting and neurological manifestations. The urine has the characteristic odor of maple syrup. The acute episode may be precipitated during a concurrent illness or during an abrupt increase in protein intake.[151] Branched-chain keto-acid oxidation is deficient but not as severe as in the classical form but the exact nature of the defect is not clear.[152] During acute attacks peritoneal dialysis and a restricted branched-chain amino acid diet is recommended. A low protein diet during asymptomatic periods should be maintained as a preventive measure.[151]

A mild form of MSUD has been described[153] in an infant with defective branched-chain keto-acid oxidation with elevated plasma and urine levels of valine, leucine, isoleucine, alloisoleucine and their keto-acid analogues. Dietary administration of branched-chain amino acids caused a further increase in the plasma and urine levels and mild symptoms of irritability and vomiting occurred.

Dietary restriction of branched-chain amino acids corrected the chemical abnormalities.

Another milder variant of MSUD has been treated successfully with thiamine.[154] The multi-enzyme complex utilizes thiamine as one of its cofactors.[147] In the thiamine-responsive form of disease it may be that the defect is related to decreased thiamine-binding.

Hypervalinemia[155] occurs because of a deficiency of valine transaminase[156] and is manifested by vomiting, lethargy, failure to thrive, mental and physical retardation, nystagmus, and increased urine and plasma levels of valine. Clinical symptoms and hypervalinemia can be corrected by a low valine diet.[157]

Hyperleucine-isoleucinemia[158] is due to a partial defect in leucine and isoleucine transamination. The clinical manifestations are failure to thrive, mental retardation, convulsions, retinal degeneration, apparent nerve deafness, and increased plasma levels of leucine and isoleucine. Leucine loading increases plasma leucine levels higher and longer than normal. Restriction of dietary protein or leucine and isoleucine reduces plasma amino acid levels to normal.

Lysine intolerance is due to a deficiency of the enzyme lysine dehydrogenase which is involved in the lysine metabolic pathway.[159] This deficiency is believed to result in lysine accumulation with consequent inhibition of the enzyme arginase, resulting in impairment of the urea cycle.[160] This results in hyperammonemia with nausea, vomiting and lethargy. Therapy consists of a low protein or low lysine diet.[161] It has been suggested that wheat can be used in the diet because of its relatively low lysine content.[161]

Persistent hyperlysinemia is characterized by elevated plasma and urinary concentrations of lysine,[162] mental retardation, muscular hypotonia and lax ligaments. After oral lysine loads, plasma lysine rises higher and longer than in control subjects. In some patients there are no abnormal clinical manifestations.[163] In some patients there appears to be a deficiency of lysine:α-ketoglutarate reductase.[164]

The *methionine malabsorption syndrome,* or oasthouse urine disease, has been described in two patients with white hair, edema, hyperpneic attacks, convulsions, mental retardation and urine that had the odor of dried celery.[165] One infant died. The second infant had diarrhea with the ingestion of methionine and the stools contained large amounts of methionine.[166] It was concluded that this condition resulted from a defect in methionine absorption. The second patient was treated with a methionine-restricted diet which controlled the diarrhea and caused disappearance of the convulsions and urinary odor.[167] The mental retardation persisted, however.

In certain susceptible children *leucine has been found to cause hypoglycemia.*[168] This group of children was separated from a larger group of children who had previously been diagnosed as having idiopathic hypoglycemia of childhood.[169] In this group of children leucine appears to cause an increased release of insulin.[170] Although a low leucine diet is effective,[171] sodium glutamate or diazoxide (or both) is a more convenient agent for treatment.[172,173] In patients with islet cell neoplasms, hypoglycemia may develop following leucine ingestion.[174] Infrequently adult patients have hypoglycemia related to leucine sensitivity.[172] Hypoglycemia in such patients is aggravated by a high protein, low carbohydrate diet.[172] Leucine can potentiate the action of sulfonylurea compounds and lower blood glucose levels in normal subjects.[175]

After eating Chinese food some persons note the onset of a syndrome characterized by a burning sensation, facial pressure, headache and chest pain.[176] This so-called *Chinese restaurant syndrome* has been attributed to the monosodium glutamate added to the food.[176,177]

Leucine, valine, isoleucine, threonine and methionine are metabolized ultimately by way of a common pathway, the propionic acid pathway.[178,179] The contribution of leucine is relatively small. Thymine also is catabolized to form propionic acid. Defects of enyzmes in this pathway may give rise to a variety of rare conditions. *Propionic acidemia* occurs when there is a deficiency of propionyl-CoA carboxylase, a biotin-dependent enzyme. This results in the accumulation of propionic acid and its metabolites, butanone, pentanone and hexanone.[180,181] The condition is manifested by recurrent attacks of ketoacidosis and neutropenia aggravated by infections and a high protein diet. The condition has variable severity ranging from death to relatively mild symptoms with mental retardation.[182] Treatment has been accomplished using a low protein diet.[183] In one patient with propionic acidemia, pharmacological doses of biotin were found to be effective.[184]

Defects in the enzymes methylmalonyl-CoA mutase, a vitamin B_{12}-dependent enzyme and methylmalonyl-CoA racemase cause *methylma-*

lonic aciduria (MMA). The condition is manifested by severe ketoacidosis soon after birth or in early infancy, failure of growth and development, protein intolerance, neutropenia and in many cases death.[185,186] In the enzyme deficient forms of MMA there are defects in the apoenzymes and therefore the apoenzyme deficient types are not vitamin B_{12} responsive.[185,186] Treatment of these diseases consists of restricting dietary protein or a combination of dietary valine, thymine and propionate. There are two vitamin B_{12}-responsive forms in which there is a defect in the synthesis of the vitamin B_{12} coenzyme deoxyadenosylcobalamin or both deoxyadenosylcobalamin and methylcobalamin.[185,186] Treatment of these two forms of MMA is accomplished with pharmacological doses of vitamin B_{12} in many cases.

Isovaleric acidemia occurs in early infancy. In this disease there are severe metabolic acidosis, ketosis, lethargy and neurological symptoms, and death may occur. Mental retardation may result in untreated patients.[187,188] The urine usually has a pungent sweat-like odor caused by isovaleric acid. Isovaleric acid is increased in concentration in the serum and urine. There is a defect in isovaleryl-CoA dehydrogenase. The condition is treated with a restricted leucine intake[188] or a low protein diet.[188]

β-Methylcrotonylglycine, β-hydroxyisovalericaciduria is caused by a deficiency of a biotin-dependent carboxylase in the leucine catabolic pathway. One patient with this disease had urine that had the odor of cat's urine due to the presence of β-methylcrotonylglycine and β-hydroxyisovaleric acid.[189] The patient had muscular hypotonia and atrophy and retarded motor development. The restriction of dietary leucine decreased the β-hydroxyisovaleric acid but did not alter the excretion of β-methylcrotonylglycine.[190] In a second patient[191] vomiting, irritability, a skin rash and acidosis occurred. Only β-hydroxyisovaleric acid was increased in the urine. The patient's condition responded to pharmacological doses of biotin (10 mg per day).

In *α-methylacetoacetic α-methyl-β-hydroxybutyricaciduria* there is late onset intermittent metabolic acidosis. The urine has increased amounts of α-methyl-β-hydroxybutyric acid, α-methylacetoacetic acid and n-butanone. These metabolites increase further with increased dietary protein or isoleucine. The acidosis is controlled by a low protein, high calorie diet.[192,193] The disorder is caused by a defect in the catabolism of isoleucine.

Hereditary tyrosinemia is caused by a deficiency of p-hydroxyphenylpyruvic acid oxidase which transforms p-hydroxyphenylpyruvic acid into homogentisic acid[194] in the tyrosine metabolic pathway. The acute form of the disease occurs in the first six months of life. Most of the patients die of liver failure.[195] The urine has a cabbage-like odor[196] probably due to a methionine derivative. The islets of Langerhans are hyperplastic and associated hypoglycemia occurs. In the chronic form nodular hepatic cirrhosis, islet cell hyperplasia, hypoglycemia, nephropathy and failure to thrive occur.[197] The nephropathy causes a Fanconi syndrome and hyperphosphatemic rickets. The urine contains large amounts of tyrosine, p-hydroxyphenylpyruvic acid and p-hydroxyphenyllactic acid,[198] and blood tyrosine and methionine concentrations are elevated. There is increased formation and excretion of δ-aminolevulinic acid and symptoms similar to those of acute porphyria are seen. Catecholamines are increased and may cause hypertension.[199] Restriction of dietary tyrosine, phenylalanine and methionine is beneficial in treating this disease.[200,201] Care must be taken not to restrict dietary amino acids too severely since amio acid deficiency may develop.[202]

In *histidinemia* there may be mental retardation and speech abnormalities but their relationship to the histidinemia is unclear.[203] Blood histidine is elevated while serotonin levels are decreased.[204] In this disease there is deficiency of L-histidine ammonia-lyase (histidase).[205] Although there have been treatment failures with a restricted histidine diet,[206] successful control can often be accomplished.[204,207,208] However, recent studies suggest that histidinemia may be benign and that dietary therapy may not be necessary.[208]

In *type I hyperprolinemia* there is a deficiency of proline oxidase which converts proline to Δ'-pyrroline-5-carboxylic acid (PC) which results in elevated blood proline levels and which may be associated, but not always, with mental retardation, renal disease and seizures.[209,210] The exact relationship between the enzyme defect and the clinical manifestations is not clear. *Type II hyperprolinemia* is due to a defect in PC dehydrogenase[211] and causes elevated blood proline and may be associated with mental retardation and seizures although the exact relationship is unclear.[211] Plasma proline levels can be decreased to normal in both of these conditions using a restricted proline intake.[209] In one patient the

associated seizures and intestinal dysfunction were also controlled with a restricted proline diet.[210]

Lipid-Induced Food Intolerance

In Table 4 various conditions are listed in which lipid intolerance occurs.

Steatorrhea occurs whenever lipid malabsorption occurs.[212,213] Steatorrhea represents an intolerance to dietary lipid. Lipid malabsorption occurs in pancreatic insufficiency,[108] various types of small intestinal diseases,[212,213] hepatobiliary disease,[212,213] the short-bowel syndrome,[214] lymphatic obstruction and intestinal lymphangiectasia,[215] mesenteric artery insufficiency,[216,217] and pancreatic endocrine diseases such as diabetes mellitus[218] and the Zollinger-Ellison syndrome.[219] Various nonpancreatic endocrine diseases also may cause malabsorption.[212] Although lipid has been thought to provoke symptoms in gall bladder disease several studies have been unable to corroborate this belief.[220,221]

In *type 1 hyperlipoproteinemia* there is severe fasting hyperchylomicronemia, pronounced elevations of plasma triglyceride, eruptive xanthomas on the skin and recurrent episodes of abdominal pain due to pancreatitis.[222] The condition is caused by an absence of lipoprotein lipase.[223] A low fat diet can control the disease process.[222] A patient with a deficiency of apolipoprotein C-II has been described in whom lipoprotein lipase activity was deficient.[224] Apolipoprotein C-II is a component of chylomicrons and is an essential activator of lipoprotein lipase.[225] Replacement of apolipoprotein C-II was effective in activating lipoprotein lipase.[224] In *type V hyperlipoproteinemia* there are hyperchylomicronemia and elevated plasma triglyceride levels.[222] Dietary treatment involves a low fat diet and weight reduction by means of a reduced caloric intake.[222]

Carnitine palmitoyltransferase deficiency is a rare disorder of muscle which causes rhabdomyolysis and recurrent myoglobinuria. The enzyme deficiency results in an impairment of fat oxidation. Hypertriglyceridemia is present in this disorder.[226,227] Complete[226] and partial deficiency[228] of the enzyme has been reported. Exercise, fasting especially with exercise, and a low carbohydrate diet can provoke attacks of rhabdomyolysis. The condition can be managed by providing a low fat diet similar to that used for patients with type I hyperlipoproteinemia.[228]

Tangier disease is characterized by the absence of plasma high-density lipoprotein and the ac-cumulation of cholesteryl esters in the cornea, peripheral nerves, and the reticuloendothelial cells of the tonsils, spleen, bone marrow, lymph nodes, thymus, intestinal mucosa and skin.[229,230] Abnormal high density lipoproteins are found in the plasma and appear to be abnormal products of chylomicron metabolism[231] which are phagocytosed by macrophages of the reticuloendothelial system.[231] Restriction of dietary fat reduces the level of the abnormal lipoproteins.[231]

In persons who are unable to metabolize the branched chain lipid phytanic acid, a chronic

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TABLE 4.—*Lipid-Induced Food Intolerance*

Malabsorption syndromes
Pancreatic insufficiency
   Cystic fibrosis
   Pancreatitis
   Carcinoma
   Other causes
Small intestinal disease
   Tropical sprue
   Celiac disease
   Regional enteritis
   Scleroderma
   Lymphoma
   Collagenous sprue
   Mastocytosis
   Multiple small intestinal diverticula
   Amyloidosis
   Immunoglobulin deficiency with lymphoid nodular
      hyperplasia
   Macroglobulinemia with infiltration of the bowel wall
   Short bowel syndrome
   Other causes
Hepatobiliary disease
Lymphatic disease
   Whipple disease
   Lymphangiectasia
   Lymphatic obstruction
   Other causes
Vascular disease
Pancreatic endocrine disease
   Diabetes mellitus
   Zollinger-Ellison syndrome
Nonpancreatic endocrine disease
   Carcinoid
   Thyrotoxicosis
   Medullary carcinoma of the thyroid
   Hypoparathyroidism
Hyperchylomicronemia
Type I hyperlipoproteinemia
   Lipoprotein lipase deficiency
   Apolipoprotein C-II deficiency
Type V hyperlipoproteinemia
Hypertriglyceridemia due to carnitine palmitoyltransferase deficiency
Tangier disease
Refsum disease due to phytanic acid α-hydroxylase deficiency
Sitosterol intolerance

slowly progressive neurological syndrome called *Refsum disease* (heredopathia atactica polyneuritiformis) occurs.[232] A diet deficient in phytanic acid, which is present in dairy and ruminant fats and which is derived from the phytol of chlorophyll, decreases the serum phytanic acid level and appears to lead to symptomatic improvement.[233]

Two sisters have been described who had elevated plasma levels of the plant steroid sitosterol, and accumulation of sitosterol in red blood cells, tendon xanthomata, adipose tissue and skin surface lipids.[234] There were lesser amounts of campesterol and stigmasterol also present. Serum cholesterol levels were normal. There was increased absorption of sitosterol by the small intestine. A sitosterol-free diet decreased the sitosterol accumulation in the patients' plasma and tissues. This rare entity has been termed *β-sitosterolemia and xanthomatosis*. The case of another patient with the same disorder and hypercholesterolemia has been reported.[235]

The relationship between dietary cholesterol and other lipids, serum cholesterol and lipoproteins, and the development of atherosclerotic coronary artery disease is a complex problem and is treated elsewhere in this symposium.

Mineral-Induced Food Intolerance

In Table 5 are listed those food intolerances related to minerals.

Sodium taken in excess may lead to hypertension. The exact relationship between sodium intake and the development of hypertension is still in dispute. It may be that sodium is an aggravating feature for those persons genetically disposed to hypertensive vascular disease. It is not possible here to review the subject in any but the most cursory fashion. However, there is some experimental and clinical evidence that implicates sodium as an important factor in the pathogenesis of hypertension.

It is known that in animals given a high sodium intake, hypertension can develop.[236] Obese patients with hypertension can be made normotensive on an isocaloric low sodium diet while a high sodium low calorie diet will result in weight loss but no change in the hypertension.[237] However, a more recent study showed a decrease in hypertension with reduction in weight without any ostensible change in dietary sodium.[238] A sodium-sensitive strain of rats has been bred.[239-242] In this sensitive strain of animals, hypertension developed with a high sodium diet and there was decreased sur-

vival. Another strain resistant to sodium was also developed. This group of animals remained normotensive on a high sodium diet and lived a normal life span. The Japanese in northern Japan have an extremely high salt intake.[243] Hypertension and strokes are common in this group. Hypertension is closely associated with sodium retaining conditions such as the Cushing syndrome,[244] primary hyperaldosteronism and other syndromes involving hypersecretion of various adrenocortical steroids,[245,246] and chronic licorice ingestion.[247] Hypertension due to primary aldosteronism or primary mineralocorticoid excess appears to be due to volume expansion secondary to sodium retention. In hypertensive states associated with secondary aldosteronism the extraadrenal stimulus causing the elevation in aldosterone leads to activation of the renin-angiotensin system.[246] A low sodium diet[248,249] or diuretic

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TABLE 5.—*Mineral-Induced Food Intolerance*

Sodium intolerance
Hypertension
Edema
    Congestive heart failure
    Cirrhosis and ascites
    Renal failure
    Cyclic edema
    Other causes
Precipitation of paralysis in familial hypokalemic periodic paralysis

Potassium intolerance
Precipitation of paralysis in familial hyperkalemic periodic paralysis
Renal failure
Addison disease
Potassium-sparing diuretic agents
Selective hypoaldosteronism
Other causes

Iron intolerance
Hemochromatosis
Dietary-induced hemosiderosis

Copper intolerance
Hepatolenticular degeneration (Wilson disease)

Iodine intolerance
Hyperthyroidism (jodbasedow)
Hypothyroidism

Calcium intolerance
Pseudoxanthoma elasticum

Phosphate intolerance
Renal failure
Tetany in infants

Fluoride intolerance
Fluorosis

therapy[249] are often successful in controlling mild to moderate hypertension. In patients with essential hypertension, sodium balance determines the degree of participation of the renin-angiotensin system in sustaining high blood pressure.[250] Even the low-renin type of hypertensive patient can become renin dependent with sufficient sodium depletion. Recently it has been shown that spontaneously hypertensive rats probably have a leak of calcium from their vascular smooth muscle membranes that is only partially compensated by the calcium transport mechanism,[251] as well as leakage of sodium, potassium and chloride.[252] Whether these defects in the rat are in any way related to possible defects in the vascular smooth muscle of humans remains to be seen.

There are, therefore, several pieces of evidence which implicate sodium as being at least one of the factors involved in the pathogenesis of hypertension, although different mechanisms may be operative in different hypertensive diseases.

Sodium aggravates edema from many causes such as congestive heart failure,[253] cirrhosis with ascites,[254] renal failure,[255] and cyclic or metabolic edema.[256] In some obese patients who fast to lose weight, significant edema develops when they resume eating.[257] This has been related to the suppression of hyperglucagonemia that occurs during fasting.[258] Glucagon has a natriuretic effect which disappears when a normal food intake results in suppression of the elevated glucagon levels. A high sodium diet may provoke paralysis in persons with familial hypokalemic periodic paralysis,[259] but this is not invariably true.[260]

Potassium can be toxic in certain special situations. Potassium may precipitate paralysis in cases of familial hyperkalemic periodic paralysis (Gamstorp disease or adynamia episodica hereditaria).[261] In renal failure potassium ingestion may aggravate preexisting hyperkalemia which can cause death.[255] Potassium may also cause hyperkalemia in such conditions as Addison disease,[262] diuretic therapy together with a potassium sparing agent (such as triamterene),[264] selective hypoaldosteronism[264-266] and so on.

In hemochromatosis *iron* gradually accumulates and leads to cirrhosis, diabetes, cardiac and pituitary disease, skin pigmentation and hypogonadism.[267-269] In this condition treatment with a low iron diet is not practical. The most efficacious therapy for hemochromatosis is phlebot-

omy.[267] Increased intake of iron can lead to so-called dietary-induced siderosis.[267,270]

In hepatolenticular degeneration or Wilson disease the accumulation of copper leads to a slowly progressive cirrhosis or cerebral degeneration (or both) and a resulting fatal neurological disease.[271-275] Treatment with a low copper diet is not practical. Treatment with penicillamine, which chelates copper and leads to a decrease in body copper stores, is quite successful and may prevent progression or development of the disease.[272]

Iodine intake may precipitate the development of hyperthyroidism, the so-called jodbasedow.[276] The mechanism whereby iodine precipitates hyperthyroidism is not certain. Persons who live in a region where iodine is deficient may have a highly effective iodine trapping mechanism within the thyroid which allows them to sequester the small amounts of iodine in their food.[276,277] When such persons move to another region where the levels of iodine are much higher or ingest iodide medication[278] or iodine-supplemented foods, hyperthyroidism may be precipitated.[276,279] The dosage of iodide[276] and the presence of thyroid disease[278] seem to be important factors in the pathogenesis of the disease. In other persons the chronic ingestion of large amounts of iodine may result in hypothyroidism.[280,281] Maternal ingestion of iodide can cause congenital goiter and hypothyroidism.[280] Often the iodides have been used as medication.[281] Myxedema has been caused by small, pharmacologic doses of iodide in patients with diffuse toxic goiter rendered euthyroid by radioiodine or surgical treatment.[281]

Calcium may be toxic in pseudoxanthoma elasticum. In this disease there is calcification of elastic fibers of the skin, retina and blood vessels leading to extensive skin lesions, progressive loss of vision and arterial disease.[282] It has been found that on a high calcium diet there is progression of the calcification which ceases when a low calcium diet is substituted.[283] Lesions can be prevented from developing in affected patients with the use of a low calcium diet. In pseudoxanthoma elasticum the abnormal elastic fibers have been shown to have an increased affinity for calcium *in vitro*.[284]

A high *phosphate* diet in renal failure may aggravate already existing hyperphosphatemia and hypocalcemia. As a result of the hypocalcemia, neuromuscular irritability and parathyroid hyperplasia occur.[285] Chronic persistent hyperphosphatemia and hypocalcemia results in stimulation

of parathyroid hormone secretion and consequent resorption of bone. In chronic renal failure there is sustained elevation of serum phosphate because of the inability of the kidney to excrete phosphate.

Control of phosphate absorption with phosphate-binding gels and use of vitamin D and calcium will decrease serum phosphate and increase serum levels of calcium.[286] Oral[287] and intravenous[288] administration of phosphate can cause a decrease in plasma calcium in hypercalcemic and normocalcemic persons. In experimental animals renal calcification can be prevented by phosphate restriction.[289] Extraskeletal calcification has been produced with orally given phosphate.[290-292] Oral administration of phosphate supplement in man and in dogs increases circulating immunoreactive parathyroid hormone.[293,294] Infants without renal failure may have tetany when fed cow's milk[295,296] which has a calcium to phosphate ratio of 1:1, compared with human milk which has a 2:1 ratio. The amount of phosphate fed exceeds the amount filtered by the kidney at normal serum levels. As a result of hyperphosphatemia, hypocalcemia and tetany occur. During pregnancy tetany and leg cramps are prone to occur in some women. Both have been attributed to the increased phosphate intake in milk together with the increased drain on calcium by the fetus.[297,298] The specific cause of the leg cramps (which occur usually between the 24th and 34th weeks of pregnancy), however, has not been established.

Fluoride is an essential trace mineral for many animals and is thought to be essential for man, although definitive proof is lacking.[299] It is well known that an excess intake of fluoride (usually in water) that naturally occurs in certain areas of the world (such as India) can cause a bone disease, fluorosis, which is characterized by osteosclerosis, periosteal new bone deposition, osteophyte formation, and ossification of tendons and ligaments. Severely fluorotic bone is friable. In this condition serum parathormone is elevated. Symptoms and signs include skeletal pain, backache, stiffness, limitation of motion of joints and flexion deformities. With a smaller intake of fluoride only mottling of the teeth may occur. A low calcium diet may cause improvement.[300] The amount of fluoride added to the water supply to prevent dental caries is well below the level of fluoride necessary to cause fluorosis or mottling of the teeth.

Other minerals are known to be essential for man. These include magnesium, cobalt, chro-

TABLE 6.—Vitamin-Induced Food Intolerance

Vitamin A toxicity
Vitamin D toxicity
Nicotinic acid intolerance
    Flushing of skin
    Abnormal findings on liver function studies
    Atypical cystoid macular edema
Carotene intolerance
    Hypercarotenemia due to 15,15'-dioxygenase deficiency
    Hypercarotenemia in hypothyroidism

mium, manganese, molybdenum, selenium and zinc. Elsewhere in this symposium the clinical importance of zinc is considered. Toxicity of these minerals usually occurs through industrial exposure and not by ingestion of the usual diet. Cardiomyopathy has been related to beer containing cobalt but other factors were implicated as well.[302] Selenium is quite toxic but toxicity does not result from ingestion of the usual diet. Selenium is an essential trace mineral serving as a cofactor of the enzyme glutathione peroxidase.[303]

Vitamin-Induced Food Intolerance

Table 6 lists those vitamins that can cause toxicity when ingested in excess amounts.

Hypervitaminosis A results from excess ingestion of vitamin A.[304,305] This is characterized by hair loss, desquamation, pigmentation, hepatomegaly, fatigue, insomnia, and bone or joint pain. Excess ingestion of vitamin D in infants and children results in hypercalcemia, anorexia, nausea, vomiting, weight loss and azotemia.[306,307] In adults, polyuria, dehydration, hypokalemic alkalosis, mental confusion, azotemia, bone resorption and metastatic calcification may occur as well.[308]

Nicotinic acid has been used in pharmacological amounts (1.5 to 9 grams per day) to treat patients with hyperlipoproteinemia (types II, IV, and V).[309] In some patients vasodilation of skin capillaries will develop with flushing and an increased skin temperature which can be uncomfortable, therefore limiting the use of nicotinic acid.[310-312] In some patients abnormal findings on liver function tests may occur although no histological abnormality occurs. Rarely jaundice will occur. Large doses of nicotinic acid also have been reported to cause pruritus, abdominal discomfort, hyperuricemia, hyperglycemia and postural hypotension. These effects are probably chemical effects and unrelated to the vitamin function of nicotinic acid. Atypical cystoid macular

TABLE 7.—*Multiple Food Intolerances*

Anorexia nervosa
Malabsorption syndromes
Food allergies
Splanchnic vascular insufficiency
Anorexia in systemic illnesses
Primary disorders of smell and taste
Nutritional recovery syndrome
Adult formiminotransferase deficiency
Gustatory sweating
Psychological disturbances

edema with loss of central vision has been reported also in patients using pharmacological amounts of nicotinic acid.[313] Vision improved and macular edema resolved with discontinuation of the nicotinic acid administration.

Hypercarotenemia has been described in a few patients who had a deficiency of the enzyme 15,15'-dioxygenase which cleaves β-carotene into vitamin A.[314] Absence of this enzyme results in the absorption of carotene and the subsequent discoloration of the skin. Hypercarotenemia should not be mistaken for jaundice since the sclerae are not affected in hypercarotenemia. The 15,15'-dioxygenase is regulated by thyroid hormone. In hypothyroidism, therefore, hypercarotenemia will develop depending on the level of β-carotene in the diet.[315]

Multiple Food Intolerances

Multiple food intolerances are common medical problems. In Table 7 certain examples of multiple food intolerances are tabulated. In *anorexia nervosa* the person rejects food in general and is unable to maintain normal body weight. Various psychiatric interpretations have been given to explain the pathogenesis of anorexia nervosa.[316-320] As yet, however, the cause is not known.

In the various *malabsorption syndromes* listed in Table 4 many different foods may contribute to diarrhea and steatorrhea. In a rare condition, *adult formiminotransferase deficiency*, there are multiple food intolerances.[321] In this condition the enzyme formiminotransferase is deficient in the jejunum, liver and red blood cells, at least. Formiminotransferase transforms tetrahydrofolate into the formimino derivative. Formiminoglutamic aciduria is present even without histidine loading. We have carried out studies in a patient with this condition in whom there was failure of jejunal glycolytic enzymes to adapt to dietary carbohydrates. Dietary carbohydrates induced

anorexia, nausea, vomiting, diarrhea, lightheadedness and syncope. In addition, various proteins caused diarrhea. The exact relationship between the formiminotransferase deficiency and the food intolerance is unclear.

As already discussed, various foods are thought to cause illness because of *allergy*. A person may be sensitive to a number of foods. Although an allergic mechanism may be invoked it is not always clear that the food intolerances are indeed caused by an allergy.

Splanchnic vascular insufficiency can cause abdominal pain after eating.[322] This is a nonspecific food intolerance and is not related to any particular food substance. The abdominal pain in this condition is the result of gastrointestinal ischemia.

Another type of multiple food intolerance is that which occurs with various systemic diseases of an acute or chronic nature in which *anorexia is a nonspecific symptom*. Anorexia occurs in a great number of illnesses, especially acute and chronic infections and inflammatory conditions and in neoplastic diseases.[323,324] The mechanism of anorexia in these conditions is not well understood. It has been postulated that in neoplasia the tumor cells produce anorexigenic peptides.[325] Primary disorders of smell and taste may cause an aversion to food. *Dysgeusia or anosmia* may lead to food rejection.[326] Treatment with zinc sulfate has been advocated for this disorder;[326] however, not all of the affected patients can be treated successfully with zinc sulfate.[327,328] This problem is discussed more fully elsewhere in this symposium.

Psychological disturbances may lead to food rejection or food faddism.[329] Food preferences, however, are conditioned by socioeconomic-cultural-religious factors.[330-331] Neuroses and psychoses may be associated with abnormalities of food intake.[332] Psychological disturbances often have been invoked to explain the compulsive eating that leads to obesity.[333,334] The problem of obesity is discussed elsewhere in this symposium.

Persons who are fasting or starving will become ill if they quickly resume a normal dietary intake.[335] This condition has been termed the *nutritional recovery* syndrome and is characterized by abdominal distention, ascites, hepatomegaly, splenomegaly, hypertrichosis, parotid swelling, gynecomastia and eosinophilia. Nausea and vomiting may also occur.

Facial sweating may occur in certain people

TABLE 8.—*Therapy for Food Intolerance*

Identify the offending food or food component

Treat the basic disease if food intolerance is a secondary consequence

Avoid the offending food or food component

Increase the activity of any deficient enzyme, if possible

after eating different foods.[336] This is particularly true in patients with diabetic autonomic neuropathy. Ingestion of cheese particularly may result in *gustatory sweating*. Atropine and oral cholinergic drugs may be successful in controlling this condition.[337]

Idiopathic Food Intolerance

Finally, we must consider those foods which cause illness for unknown reasons. It is not possible to consider every food that has been reported to cause symptoms or illness. It is difficult to determine what component or components of a given food cause the difficulty. Some of the foods that are reported to cause illness include liver, chicken, beets,[338,339] cucumbers, Worcestershire sauce[340,341] and curry.[342] A large number of people dislike liver and many report that liver causes nausea and vomiting or diarrhea. Some patients are intolerant of chicken. In a rare patient beets have caused shock with the appearance of beet pigment (betanin) in the urine.[338,339] Similarly, cucumbers have been reported to cause shock. There is a question as to whether the heavy use of Worcestershire sauce may cause renal disease.[340,341] There are suggestions that the use of curry may cause renal damage.[342] Anaphylactic shock is well described in certain persons who are sensitive to nuts and shellfish.[89] In many instances the reports of food intolerance are anecdotal and poorly documented.

Therapy for Food Intolerance

When faced with the problem of food intolerance the systematic approach outlined in Table 8 is a convenient plan to follow. The offending agent in the food or the particular nutrient itself should be identified, if possible. If the food intolerance is secondary to a particular disease this should be treated. In primary food intolerance the offending agent or food can be avoided, if known. When using low protein diets one must be careful not to restrict the protein intake to such low levels that protein deficiency occurs. One must take special care when using diets that are defi-

cient in one or more specific amino acids that the restriction is not so severe as to impair protein synthesis.

In some cases of food intolerance it is possible to increase the activity of a deficient enzyme responsible for the food intolerance by the use of a particular nutrient which will cause an adaptive increase in enzyme activity. Since the deficient enzyme is probably defective in structure its activity will not reach normal levels but may increase sufficiently so as to increase the tolerance of the person to the particular offending nutrient. Such an approach has been used in treating sucrase-isomaltase deficiency with fructose[20] and hereditary fructose intolerance and fructosediphosphatase deficiency with folic acid.[24,28-30] It is also important to restrict the foods that contain the offending nutrient. The adaptive increase in the deficient enzymes may give some measure of protection against the inadvertent ingestion of the otherwise toxic nutrient.

The subject of food intolerance is quite complex. Only the broad outline of the subject has been presented here. Clearly, nutrient substances may cause illness so that one can truly say that "One man's meat is another man's poison."

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